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TETRA-ETHYL LEAD POISONING

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Tetra-ethyl lead is the active ingredient of ethyl fluid, an anti-knock compound which for many years past has been widely used by the oil industry for addition to petrol. The toxic properties of tetra-ethyl lead are well known and have been very completely investigated and described—notably by Kehoe—following the occurrence of cases of poisoning when the manufacture of this substance was begun on a commercial scale in the United States in 1924. The absence hitherto of any cases of tetra-ethyl lead poisoning in this country has probably distracted attention from the possibility of its occurrence, and it may be timely to show how it can occur and to recall the symptoms, diagnosis, and treatment of the condition.

Properties of Tetra-ethyl Lead.—Owing to its ready miscibility with fats and oil, tetra-ethyl lead can be absorbed through the intact skin. The vapour given off is readily absorbed through the pulmonary epithelium, and though the substance is of low volatility its vapour pressure is of great significance toxicologically, since it is chiefly from inhalation of the vapour that poisoning is liable to occur. Air saturated with its vapour at ordinary temperatures contains approximately 5 mg. of lead per litre. Its toxicity is a function of the lead content and not of any peculiar qualities characteristic of the compound, but its fat-soluble character allows selective localization in the nervous tissues of the body, and for this reason tetra-ethyl lead poisoning is essentially a central nervous system intoxication (Kehoe, 1925, 1927).

Aetiology

The risks of tetra-ethyl lead poisoning occur, first, in the manufacture of tetra-ethyl lead and of ethyl fluid, the latter containing 60% by weight of tetra-ethyl lead and being the form in which the compound is added to petrol; and, secondly, in the blending of ethyl fluid with petrol. These processes, however, are so well controlled and their hazards so fully understood and so vigilantly guarded against that the occurrence of other than the mildest manifestations of lead absorption is very rare in the manufacture of the product and virtually unknown in lead-blending (Kehoe, 1934; Kehoe and Machle, unpublished data, 1936).

In addition the hazard involved in the cleaning of storage tanks which have contained leaded petrol has long been recognized. A sediment which can be likened to a muddy sludge is deposited on the bottom of every bulk-petrol-storage tank after a period of time. When leaded petrol is stored this sludge contains organic lead compounds and as a result is highly toxic in the same way as is concentrated tetra-ethyl lead, and may, from inhalation of its vapour during cleaning operations, give rise to similar acute and fatal illness. Machle (1935) reports 11 out of 17 cases of lead poisoning as occurring in this way between 1930 and 1935 in the United States.

The possibility of the occurrence of lead poisoning in the distributive and allied trades and among the general public

from the use of leaded petrol, where the concentration of lead has not exceeded approximately 1 in 1,300, has been widely investigated and uniformly discounted (Kehoe, Thamann, and Cholak, 1934, 1936; Final Report of Departmental Committee, 1930; Lind, 1936). Thus in the consideration of tetra-ethyl lead poisoning it is important to distinguish between contact with the concentrated products which are potentially toxic and the diluted leaded petrol which in normal concentrations is relatively innocuous.

In this country up to 1940 the only opportunity of contact with the concentrated product was in the blending of imported ethyl fluid with petrol. Blending was carried out in several refineries and depots throughout the country by a group of some 300 men. The process of blending was a standardized one, and in addition the men were under careful medical supervision. No cases of lead poisoning or any clinical evidence of lead absorption were noted among this group up to 1943. Laboratory workers were similarly controlled, and were equally free from toxic effects (Boldero and Robertson, personal communication).

After the outbreak of war the opportunities of contact with tetra-ethyl lead in this country increased. The manufacture of tetra-ethyl lead and of ethyl fluid was begun in 1940, and has been carried on ever since; but, under the most carefully controlled plant conditions and with very complete medical supervision, including regular laboratory investigations, no cases of poisoning have occurred. The workmen, tested before employment, showed a mean urinary lead excretion of 0.0328 mg. per litre. With exposure to lead this had risen a year later to 0.0774 mg. per litre, but with improvement in technique and with experience it had fallen in a further year's time to 0.0562 mg., and has remained in this region for the past four years, the latest figure being 0.0493 mg. per litre. Furthermore, the amount of ethyl fluid blending increased for a time, but laboratory analysis of urine samples from 1943 onwards showed no evidence of lead absorption attributable to this operation, nor did medical examination reveal any clinical evidence of lead intoxication.

Thus experience in this country followed that of the United States in the absence of toxic sequelae from the manufacture and handling of the concentrated products once the dangers were understood and the hazards controlled.

Throughout the war all aviation petrol contained tetra-ethyl lead, and from approximately the beginning of 1942 all petrol used by the Armed Forces, and to a large extent by the civil population also, contained that substance. During the war, however, many operations involving the handling, packing, and distribution of such petrol—much of it in small containers—had to be carried out under conditions which would not have been tolerated during peacetime. Much of the work was done by hand under security conditions of black-out precautions and

blast protection, which seriously interfered with the basic safety measures of effective ventilation.

Can-filling; Can-washing

Reports from abroad of certain cases of lead poisoning, characterized by the sudden onset of cerebral symptoms and occasionally ending fatally, drew attention to the possible hazards connected with the filling of very large numbers of petrol cans under conditions of operation described above.

Although it was realized that the absence of tropical conditions and the intermittent nature of the work rendered less likely the occurrence of such cases in this country, an investigation of can-filling was carried out in two localities in Britain. No cases showing clinical signs or symptoms attributable to tetra-ethyl lead poisoning were uncovered, but laboratory analysis of urine samples from a random selection of male and female can-fillers and can-washers showed that lead was present in such concentration as to point to a possibly hazardous lead exposure (Table I). Furthermore, estimation of the

TABLE I.—Frequency Distribution of Can-fillers and Can-washers According to Milligrammes of Lead per Litre of Urine

Mg. Lead	Nov. to Jan.		Jan. to March		March to May	
	Fillers	Washers	Fillers	Washers	Fillers	Washers
0-0.025 ..	—	—	—	—	—	—
0.026-0.050 ..	—	—	—	2	1	3
0.051-0.075 ..	1	1	1	3	2	6
0.076-0.100 ..	2	5	1	5	4	7
0.101-0.125 ..	3	3	4	1	5	4
0.126-0.150 ..	7	4	7	3	7	7
0.151-0.175 ..	5	1	1	—	1	1
0.176-0.200 ..	5	4	3	3	1	3
0.201-0.225 ..	2	3	3	2	2	—
0.226-0.250 ..	3	4	2	2	2	1
0.251-0.275 ..	1	3	1	1	2	—
0.276-0.300 ..	2	3	—	3	—	—
0.301-0.325 ..	3	4	1	—	—	—
0.326-0.350 ..	—	—	1	3	—	—
0.351-0.375 ..	1	1	—	—	—	—
0.376-0.400 ..	—	2	—	—	—	—
0.401-0.425 ..	1	—	—	—	—	—
0.426-0.450 ..	—	—	—	—	—	—
0.451-0.475 ..	1	—	—	—	—	—
0.476-0.500 ..	—	—	—	—	—	—
0.501-0.525 ..	—	—	—	—	—	—
0.526-0.550 ..	—	1	—	—	—	—
0.551-0.575 ..	—	—	—	—	—	—
0.576-0.600 ..	—	1	—	—	—	—
Total ..	38	40	25	28	27	32
Mean ..	0.2051	0.2267	0.1730	0.1728	0.1417	0.1091
Standard deviation ..	±0.0951	±0.1185	±0.0695	±0.0987	±0.0609	±0.0484
Prob. error of mean ..	±0.0103	±0.0126	±0.0095	±0.0128	±0.0079	±0.0057

amount of lead in the atmosphere showed a higher concentration than was considered desirable for prolonged periods of work in the buildings concerned, being higher than the safe limit of 1.5 mg. of lead per 10 cubic metres of air defined by the American Public Health Association (1943) (Table II).

TABLE II.—Average Concentration of Lead in Atmosphere in Can-filling Buildings in Milligrammes of Lead per 10 Cubic Metres of Air

	Plant X		Plant Y	
	Day	Night	Day	Night
Face level ..	11.9	4.78	5.21	2.26
Random point in building ..	4.65	3.37	1.2	1.2

Conditions were much improved by the installation of more efficient ventilation, by the introduction of mechanical filling, and by the enclosure of the filling machine, the average amount of lead in air being reduced to 2 mg. per 10 cubic metres. Gradual diminution in the urinary lead concentrations of the operators then occurred, and this was further hastened in the case of can-washers by the substitution of unleaded fuel in washing out the cans—a step which had the additional effect of reducing the amount of lead in the atmosphere of their building to 1 mg. per 10 cubic metres. Urine analysis, continued for a few months after these operations had ceased, showed a further drop in the mean lead urinary concentration to 0.08 mg. per litre.

Thus although there were no clinical symptoms of lead poisoning the degree of lead absorption was potentially toxic, and could only have derived from exposure to leaded petrol.

Other Refinery Operations

It was thought, too, that the conditions under which petrol had to be handled from time to time gave rise to increased lead absorption by other refinery operators, since some men, who were giving urine samples on account of occasional ethyl fluid blending, began to show higher urinary lead concentrations than the operation of blending could explain, especially since the amount of blending had by then greatly diminished.

Such men were engaged in tank-dipping, in the filling of road and rail cars, and more especially in attending to the pumps in underground or semi-underground pump-houses. Here some leakage of petrol always occurred and the atmosphere smelt strongly of spirit; nor were the men too careful in running the ventilation system, especially in winter-time. Some of these men showed mild symptoms of intoxication, as evidenced by disturbance of sleep and the occurrence of fantastic dreams, while at the same time they had urinary lead concentrations as high as 0.275 mg. per litre. Two of the men for a time compared their dreams each morning; another expressed himself as unable to compose his mind sufficiently to go to sleep. No more serious manifestations occurred, however, and with the success of the Normandy campaign the handling of large quantities of such fuel, and consequently the amount of exposure, diminished very considerably and the symptoms disappeared.

Lead absorption also seemed to be greater in operators at those depots which, for safety's sake, had been built below the level of the surrounding countryside and in which, as a consequence, natural ventilation was poor. Thus while the mean urinary lead concentration of all the lead-blenders in the country was 0.0535 mg. per litre (± 0.0338), that of the operators in two such depots was 0.157 and 0.188 mg. per litre. On clinical examination these men showed no evidence of lead intoxication, and would have attracted no attention had not their urinary lead figures been so much higher than normal.

Tank-cleaning

After the cessation of hostilities a number of tanks which had been specially constructed for war purposes, and notably those which had contained aviation petrol, were no longer required in service. Accordingly it was decided to close them down after they had been cleaned. It was known that the sludge on the bottom of all these tanks contained organic lead compounds and that the operation of cleaning required strict observance of precautions designed to protect workmen from exposure to these compounds. The sludge was present in all storage tanks which had contained leaded petrol, irrespective of the lead concentration of the fuel; it contained organic lead compounds varying in amount from 0.044 to 0.084% in a series where analysis was carried out. The vast majority of the tanks in question were underground, and for this reason they presented far more serious cleaning problems than those normally associated with the usual type of bulk-petrol-storage tank built above ground.

Briefly, the operation of tank-cleaning consisted in sweeping the floor and scraping the sides and supporting pillars of underground tanks of 500, 2,000, and 4,000 tons capacity after the petrol had been pumped out and the air rendered gas-free by ventilation. Men engaged in the work were required to wear an air-line mask and were supplied with a complete outfit of clothing, including boots, gloves, and headgear. A warm bath was provided at the end of the day before the ordinary clothing was resumed.

The programme of tank-cleaning was begun in different parts of the country in the autumn of 1945, and in some instances the regulations governing the cleaning procedure came to be overlooked or disobeyed, with the result that several cases of poisoning occurred, while elsewhere the operation was carried through for months without even the mildest lead absorption resulting.

In all, there occurred twenty-five cases of tetra-ethyl lead poisoning of varying severity, two of them being fatal. Of four very severe cases, three occurred in foremen or charge-hands.

Case Histories

Case 1.—Aged 42. Started tank-cleaning on Oct. 31. After two weeks he was suffering from lack of appetite and broken sleep, and his mates thought he looked ill. He had a long week-end break and resumed work on Nov. 20 for a further week, during which he slept badly and had troublesome dreams, in one of which he had constantly to be brushing rats off his chest while he lay in bed. He felt sick, but couldn't vomit. On Nov. 28 his behaviour became odd in that he interfered with the apparatus used by the other men and complained of a loss of money which he had not in fact sustained. In the evening he became noisy and violent, and appeared to be having fits. He was admitted to hospital in the early morning of Nov. 28, and was found to be in a convulsion, deeply cyanosed, with an almost imperceptible pulse; he died within 15 minutes of admission. At necropsy a few white patches were seen on the arachnoid which were reported as suggestive of leptomeningitis or of lead or alcoholic poisoning. Sections of liver, kidney, spleen, stomach, and brain showed only the general appearances of degenerative change of varying severity. Analysis of the organs for lead showed the following, in milligrammes of lead per 100 g. wet tissue: brain, 0.74; liver, 2.35; spleen, 0.29; kidneys, 0.79. Normal maximum concentrations of lead in these tissues may be taken as brain, 0.09; liver, 0.28; spleen, 0.07; kidneys, 0.16 (American Public Health Association, 1943). Since tank-cleaners at this time were not under medical supervision, no sample of urine was available for analysis, but the quantity of lead found in the tissues, along with the symptoms described, left no doubt that the cause of death was acute lead poisoning.

Case 2.—Began tank-cleaning on Oct. 31, and first complained of sleeplessness on Nov. 16. He had a week-end break, during which he was restless by day, slept badly, and suffered from a mild diarrhoea for two days. He resumed work on Nov. 20 and continued to have insomnia. A few days later his letter home to his wife was confused and queer; he contradicted himself in it several times. He continued at work until Nov. 29, when he became rambling in his talk. He said he felt very weak and that he must go off and rest. He was admitted to hospital later on the same day, restless and violent. He was confused, amnesic, and disorientated in time and place. He was suspicious, impulsive, violent, and suicidal, requiring continuous strict nursing supervision. His blood pressure was 108/60 while violent, the lowest reading being 94/60 during a quiet spell. The pulse rate ranged from 72 to 84, and his temperature was subnormal. Superficial reflexes were brisk, deep reflexes diminished, plantar responses flexor; cranial nerves appeared normal. There was some incontinence of urine, and later a double incontinence. Blood examination showed 4.65 million red cells, 94% haemoglobin, 8,750 white cells, and no punctate basophilia or stippling of the red cells. Urine on Dec. 11 showed 0.440 mg. lead per litre, specific gravity 1014; on Dec. 19 0.98 mg. per litre, specific gravity 1020. Blood urea was 65 mg. per 100 ml. on Dec. 11, and 30 mg. per 100 ml. on Dec. 21. He was given glucose-saline and magnesium sulphate intravenously and received strong sedation: 40 ml. hexobarbitone intravenously between Dec. 4 and 6, 127.5 gr. (8.3 g.) "nembutal" (pentobarbitone sodium) between Dec. 4 and 18, and 14 litres glucose-saline with 21 g. magnesium sulphate intravenously between Dec. 4 and 15. His condition gradually deteriorated. He developed frequent muscular twitchings and attacks of spasticity and was restless, talkative, and hallucinated. On other days he was quieter, but gradually he became weaker and lost much weight; he was semiconscious by Dec. 24. Next day there was a marked change in his condition. He became entirely rational; the twitchings ceased; bowel and bladder control were regained; at night he slept well, and from that day he steadily improved. His blood pressure was 110/70 at this time, but a week later it was 120/80. His weight was only 7 st. (44.5 kg.). March 26 he weighed 12 st. 4 lb. (78 kg.) and his blood pressure was 140/85, pulse rate 72, temperature 98° F. (36.7° C.). His only recollection of the illness was of his dreams, in which he was usually struggling against terrific odds, but always successfully. His urinary lead was 0.086 mg. per litre, specific gravity 1013; and he complained only of slight stiffness in both knees. His condition otherwise, both physically and mentally, was normal.

Case 3.—Aged 43. Started tank-cleaning on Nov. 13, spending between five and six hours daily in the tanks. On Nov. 21 he suffered from nausea and vomiting in the evening and was off work next day. On Nov. 28 he had diarrhoea and vomiting, and was sweating and tremulous; he had difficulty in falling asleep and spent most of the night talking and smoking. He was irritable and excited. Seen next day by his doctor, he was thought to be suffering from influenzal gastro-enteritis. He spent four or five days in bed but could not sleep, or such sleep as he had was broken by frightening dreams. In one of these he was seized by an octopus and had to fight it with a knife in order to escape. He twitched during sleep. He then began to be odd in his behaviour, passing strange remarks and quoting scripture, doing everything in a great hurry and

shouting instead of talking quietly, and he seemed very nervous. On Jan. 2 he was seen by a psychiatrist, who found him confused and depressed and to have delusional ideas, and who recommended his admission to a mental hospital. By Jan. 8 he had lost between one and two stones (6–12 kg.) in weight. He was restless and somewhat inarticulate. His colour was good. His pulse rate was 48, temperature 97.2° F. (36.2° C.), and blood pressure 90/55. His superficial and deep reflexes were exaggerated. His movements were clumsy and spasmodic, but muscle power and tone were good. Mental confusion and delusional ideas were still present. Blood examination showed no punctate basophilia or polychromasia. Urinary lead concentration was 0.215 mg. per litre, specific gravity 1014, six weeks after his last exposure. He became violent a few days later and was admitted to a mental hospital in a state of acute delirious mania. During the first 24 hours he received four injections of 2 ml. of "sominifaine." On Jan. 21 he was still a little confused at times and suspicious, but he had made some progress and his blood pressure had risen to 110/60. He improved steadily and was mentally normal by Feb. 8, when his urinary lead concentration was 0.295 mg. per litre. He was discharged on April 1, mentally well and in a much improved physical condition. His urinary lead concentrations gradually diminished as follows: Feb. 18, 0.210; March 20, 0.135; May 2, 0.091; June 28, 0.063 mg. per litre.

Case 4.—Aged 31. Began tank-cleaning on Oct. 31, and had difficulty in falling asleep as early as the night of Nov. 1. He continued at work till Nov. 7, when he felt light-headed and very tired. He saw a doctor on Nov. 8 and was sent home for a week. He continued to sleep badly in spite of sedation, but his appetite was good. He returned to work on Nov. 20 and after one day felt sick and nervous and could not eat his breakfast. He returned home, where his appetite improved, but his sleep was broken by nightmarish dreams. He remained under his doctor's care till Dec. 3, when he was certified fit to resume work. On that day news of the death of a fellow workman was received, and he was re-certified as unfit for work. On Dec. 7 he looked well and had a good colour, but was a little confused mentally and apt to repeat himself. He had a fine tremor of hands and tongue. All reflexes were exaggerated except the biceps jerk, which was only just elicited. Muscle power and tone were good, pulse rate 48, blood pressure 110/55. Blood examination showed no punctate basophilia or polychromasia. The urinary lead concentration was 0.350 mg. per litre, specific gravity 1025, seven weeks after his last exposure. With ordinary convalescent treatment and mild activity in the open air, he made a good recovery and was fit for work a month later.

Case 5.—Aged 33. Started tank-cleaning on Oct. 31 and worked till Nov. 6, when he felt queer about the stomach and bought some stomach powder, after taking which he ate a good tea. He could not sleep that night and lay awake till morning. He could not eat his breakfast. He saw a local doctor and returned home to bed. He stated that he had no recollection of anything thereafter for a week or two. Seen by his doctor on Nov. 7, his case was diagnosed as "gastritis"—his appetite was poor and he had vomited several times. He slept very little even with the help of sleeping tablets until nearly a week had elapsed. He was sent to see a consultant with regard to his stomach, and was referred to a psychiatrist, who found him in a muddled anxious state just as if he was recovering from a hysterical fugue. He showed no sign of mental confusion or of organic change in the central nervous system. The picture was that of a neurosis. Blood examination on Dec. 6 showed 4.8 million red cells, 98% haemoglobin, 7,600 white cells; a few punctate basophils were seen, but not enough to justify a diagnosis of lead poisoning. A further blood examination on Dec. 7 showed no abnormality of any sort. His pulse rate was 78, blood pressure 120/80. Urinary lead concentration was 0.210 mg. per litre, specific gravity 1019, two months after his last exposure. He steadily improved in health and was fit for work a month later.

Case 6.—Aged 38. Began tank-cleaning on Jan. 2 and continued for one week. On Jan. 9 he felt sick, vomited once, and had severe diarrhoea with no abdominal pain. He had difficulty in falling asleep, and his sleep was fitful and troubled by weird, at times terrifying, dreams in which quaint human beings and animals figured. He was certified by his doctor as suffering from gastro-enteritis and did not return to work. The stomach condition settled down within a day or two, but his appetite remained poor and the sleeplessness persisted. During the day he was restless, irritable, and nervy, and wanted to be on the move all the time. On Jan. 15 his doctor thought him neurasthenic, especially as he had difficulty in passing urine from time to time. On Jan. 19 he looked better, though still anxious and apprehensive. Superficial reflexes were brisk, deep reflexes not exaggerated, muscle power and tone both good. There was some coarse tremor of hands and fingers, with some incoordination of movement. Blood pressure 112/60; pulse rate 64; urinary lead concentration 0.455 mg. per litre, specific gravity 1025. On Jan. 21 he was thought to be progressing satisfactorily since he was sleeping better and his appetite had improved. On the morning of Jan. 23 he suddenly became worse with maniacal

symptoms and delusions, trembling violently, sweating profusely, and talking incoherently. He was given 2 gr. (0.13 g.) of "luminal" (phenobarbitone), repeated in four hours, without effect; by evening he was in a state of acute mania, screaming at the top of his voice, and had to be forcibly restrained in bed. He was quite disorientated in time and place. There were no convulsions, and he died soon afterwards. At necropsy there were no changes except a few subserous petechiae in the heart and pericardium. Analysis of the organs showed the following in milligrammes of lead per 100 g. of wet tissue: brain, 0.6; liver, 2.5; spleen, 0.27; kidneys, 1.2.

Nineteen more men suffered ill effects. Nine of these at one depot had a mean urinary lead excretion of 0.249 mg. per litre, with a range of 0.110 to 0.480 mg. Their symptoms, in order of frequency, were: sleeplessness (including difficulty in falling asleep), broken sleep, and troubled dreams; a nasty sweet taste in the mouth and a bad smell to the breath; lack of appetite; diarrhoea with or without abdominal pain; trembling, shakiness, giddiness; complaint of loss of weight. On examination most of the men displayed increased deep and superficial reflexes, a slow pulse, and lowered blood pressure; some showed a tremor of hands and tongue. None showed mental confusion. There was no basophilic stippling of the red cells.

Six men at another depot, after one or two weeks of tank-cleaning, suffered from sleeplessness shortly followed by lack of appetite and, in some cases, bowel movements which were "watery and slimy—not a real motion." Here it was only after one man had consulted his doctor about insomnia and had been advised to have a change of work that mention of this symptom was made, and all discovered they had been having the same experience. They had been explaining away their sleeplessness to themselves in various ways—e.g., lack of exercise in the winter-time. The supervisor had attributed his insomnia to "worrying needlessly about the job and the men." These men, three months after ceasing this work, had a mean urinary lead concentration of 0.143 mg. per litre, with a range of 0.078 to 0.215 mg. Blood examinations at this time showed no stippling of the red cells or any other abnormality.

Four men at yet another depot showed a mean urinary lead concentration of 0.210 mg. per litre, with a range of 0.175 mg. to 0.240 mg. They had shown similar symptoms—viz., sleeplessness, anorexia, and nausea. Two of them had induced vomiting in an attempt to rid themselves of the feeling of sickness. One man had auditory hallucinations in the form of voices talking to him and people walking behind him, and was considered by his doctor to be suffering from an anxiety state, from which he took about six weeks to recover. None showed any red blood cell changes.

By contrast, 15 men who had done this same work continuously for three months under careful supervision showed a mean urinary lead concentration of 0.048 mg. per litre. The range was from 0.016 to 0.073 mg. except for one case where the figure was 0.135 mg. All these men were symptomless, all had put on weight, and their state of health was the envy of their friends and relatives.

Symptoms

The earliest symptoms in 25 cases of tetra-ethyl lead poisoning were disturbance of sleep and symptoms referable to the alimentary tract. The classical signs and symptoms of lead poisoning—viz., abdominal colic, tremors and fibrillary twitchings, myalgia, neuralgia, constipation, pallor, blue line on the gums, paralyses, stippling of the red blood cells, and punctate basophilia—either did not occur or were a very minor part indeed of the picture.

The earliest indication, often coming on within the first week of exposure, was sleeplessness. A healthy man who regularly went to sleep about 10.30 p.m., "as soon as my head touched the pillow," would lie awake till 2 or 3 a.m., sleep for an hour, often with troubled dreams, wake up with a start, and perhaps snatch another hour of restless slumber before morning, or else find the morning arrive without further sleep. Following shortly upon insomnia, only rarely preceding it, came alimentary tract disturbance—lack of appetite, nausea, vomiting, and diarrhoea of varying severity with no abdominal pain. Subjective nervous symptoms were next in evidence—such as irritability, restlessness, nervousness, and anxiety, possibly tiredness.

The signs at this time were a slow pulse, subnormal temperature, low blood pressure, increased reflexes, and a slight loss of

body weight. With longer or more severe exposure the signs and symptoms progressed to increasing tiredness and loss of body weight, tremor, muscular weakness and twitching, oddities of behaviour, and evidences of mental confusion, and then, quite abruptly, came the onset of acute maniacal symptoms with suicidal tendencies, or the occurrence of a convulsion. Machle (1935) states that in general a given patient will manifest a type of mental response characteristic for him, and not related to the severity of his illness or its stage, but apparently dependent on his mental background. We agree that this was so in this series of cases.

Pallor was not a feature of any of the cases, nor did punctate basophilia occur. Some cases had been referred to a pathologist for blood examination, on account of a suspicion that lead might be the cause of the illness, and had been reported as "not suffering from lead poisoning" because of the absence of punctate basophilia.

Diagnosis

The diagnosis depends upon the occurrence of such symptoms as have been described, along with the history of exposure to a severe lead hazard. Recognition of what constitutes a severe lead hazard is all-important.

Urinary lead concentration will give some idea of the degree of exposure. If this is less than 0.1 mg. per litre at a time when symptoms of the above nature are displayed, tetra-ethyl lead is unlikely to be the cause. Mild symptoms may occur with a figure of 0.15 mg., but generally it is above this level, and in severe cases it is more likely to be in the region of 0.3 mg. or more. Kehoe (1942) states that the upper limit of safe lead exposure as defined on the basis of urinary lead excretion of exposed workmen is represented by a mean value of approximately 0.10 mg. lead per litre for samples that exceed 0.15 mg. only infrequently and 0.20 mg. per litre rarely.

If a 24-hour sample of urine is obtained without unduly large quantities of fluids having been consumed previously, the urinary lead concentration figure may be accepted as it stands. If one single sample is analysed, varying in quantity from approximately 75 to 350 ml., its specific gravity should be taken into account in assessing the significance of the lead concentration. A procedure which has some value in this respect is to multiply the "mg. per litre" figure by 24/G, where G=1,000 (S.G. of sample, 1) (Levine and Fahy, 1945). A high lead concentration in a sample of low specific gravity obviously carries more significance than the same concentration in a sample of high specific gravity.

It is essential in collecting a sample to use a chemically clean container—not necessarily sterile—one which has been washed out with concentrated redistilled nitric acid and with doubly distilled water. One is dealing with microgrammes of lead, and unless a properly prepared container is used the figure obtained will be unduly high. In collection, the sample is passed directly into the container without using any intermediate vessel.

Among the lesions which may simulate this condition are encephalitis due to infection, neurosyphilis, unlocalized brain tumour, cerebral arteriosclerosis, uraemia, and cerebral manifestations of pellagra. Other types of cerebral intoxication caused by alcohol, mercury, carbon monoxide, and overdosage with drugs such as bromides and barbiturates must also be considered. It should be remembered that, unquestionably, severe lead exposure is required to cause lead encephalopathy in the adult (American Public Health Association, 1943).

The absence of stippling does not rule out tetra-ethyl lead poisoning; basophilic stippling of the red cells is commonly absent, and was absent in all the cases described in this series.

Prognosis.—Death may occur rapidly within a few hours of the acute onset or may be delayed for some weeks. If death does not occur within this time, recovery is usually complete. There have been no permanent cerebral sequelae in this series.

Prevention

The careful observance of regulations in carrying out all operations connected with tetra-ethyl lead will prevent the occurrence of poisoning, since the hazards are well understood and guarded against. Intelligent and unremitting supervision of the men is called for, and should be the responsibility of someone of higher status than foreman or charge-hand. One foreman, who died, neglected to take precautions and was

reported to have said that he had worked with petrol all his life and it had never hurt him. One charge-hand, another severe case, thought that fifteen years of work with petrol absolved him from the necessity for taking precautions.

Treatment

All that is necessary in the milder cases is removal from exposure, light exercise in the open air, a normal diet with plenty of fluids, and the relief of sleeplessness by adequate doses of a suitable sedative, preferably one of the barbiturates. The treatment of the severe case calls for strict nursing supervision in view of the impulsive suicidal tendencies sometimes displayed, and for adequate fluid intake and sedation.

Glucose, 5% in saline, may be given intravenously up to 3 litres per day. If given as a drip, hexobarbitone may be added. "Somnifaine" and pentobarbitone sodium are other suitable sedatives, and may be given in repeated full doses to obtain rest. A retention enema of 4 to 6 oz. (110–170 g.) of a saturated solution of magnesium sulphate often has a quieting effect when it can be retained. Morphine is contraindicated. Machle (1935) recommends the intravenous administration of from 2 to 4 g. of magnesium sulphate in 2% solution accompanied by doses of pentobarbitone sodium up to 15 gr. (1 g.) daily by mouth. Reference to Case 2 of this series will give some idea of the amount of sedation which may be required in a severe case.

Ample fluids should be given throughout subsequent convalescence to aid the elimination of lead. After a severe exposure many months may elapse before the urinary lead concentration reaches a normal figure.

Summary

The properties of tetra-ethyl lead are briefly recalled.

The opportunities to develop tetra-ethyl lead poisoning in this country are described.

Twenty-five cases of tetra-ethyl lead poisoning of varying degrees of severity occurred during tank-cleaning operations, and six of the cases are described in detail.

The symptoms, diagnosis, and treatment of tetra-ethyl lead poisoning are discussed briefly.

We are indebted to Dr. R. W. Zeitlin for his help in two of these cases, and especially for his care of one of them throughout its course to a happy conclusion; also to Dr. Stanley H. Coleman, Dr. R. E. Hemphill, and Dr. G. Schwizer for their assistance in three other cases. The chemical analytical work upon which these observations are based was carried out in the Courtauld Institute by Mr. E. R. Smith. The blood examinations were performed by Mr. R. L. Harding, and to both of these gentlemen we wish to express our thanks.

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The first number of *Anaesthesia*, the journal of the Association of Anaesthetists of Great Britain and Ireland, has now been published. It opens with a foreword by Sir Alfred Webb-Johnson, P.R.C.S., wishing the journal every success, and noting that the year of celebration of the centenary of the first operation under general anaesthesia in this country is a most opportune time for founding a journal which will make British teaching and records of discovery and achievement available for the medical profession throughout the world. The editor, Dr. C. Langton Hewer, contributes a note giving the reasons for launching *Anaesthesia*; and this is followed by an article on the inception and purpose of the Association of Anaesthetists written by Dr. H. W. Featherstone, its first president, and another, on the centenary of anaesthesia in Great Britain, by Dr. A. D. Marston, who now holds that office. The rest of the issue is taken up with short practical articles, a review, and some abstracts and items of news. *Anaesthesia* is published quarterly from 24, Thayer Street, W.1.

POST-PENICILLIN JAUNDICE

BY

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During recent years increasing numbers of cases have been reported in which infective hepatitis has been conveyed to patients by means of an infected injection. The cases fall naturally into two groups, the first of these being cases in which infected serum has been injected either intravenously or intramuscularly. Beeson (1943), Morgan and Williamson (1943), Steiner (1944), and other authors have reported the occurrence of jaundice after transfusion with whole blood or blood plasma. Similarly, hepatitis has followed administration of convalescent serum in the treatment of mumps and measles; jaundice has also occurred after yellow fever immunization where the vaccine contained human blood serum. Experimentally the disease has been transmitted to human volunteers by injection of blood or serum from patients in the pre-icteric or early icteric stages; this experimental work was summarized by McCallum (1944).

Into the second group fall those cases in which the disease may be conveyed by an infected needle or syringe. Salaman *et al.* (1944) reported a high incidence of jaundice in patients receiving intravenous injections of arsenic for syphilis at the Royal Victoria Hospital, Netley, and showed that the incidence of this condition could be much reduced by careful sterilization of needles and syringes. Sheehan (1944) reported further such cases, and considered that hepatitis following the administration of neoarsphenamine was due to the transmission of a blood-borne virus from one patient to another by unsterile syringes. Droller (1945) described an outbreak of jaundice at a diabetic clinic due to the collection of blood for blood-sugar estimation, and Sheehan (1944) reported cases following the withdrawal of blood for estimation of the erythrocyte sedimentation rate. It is here of interest to recall that Murray (1930) reported a high incidence of jaundice in patients treated with intravenous acriflavine for gonorrhoea; there can be little doubt from his description that the cases were identical with those at present under discussion.

Case Histories (Military General Hospitals)

During the past few months, while working in military general hospitals in India, it was noted with interest that a large number of cases of infective hepatitis admitted to medical wards gave a history of having received a course of penicillin injections within the previous seven months. A total of 124 cases of hepatitis were seen, and 36 of these were found to have had penicillin treatment. Clinically these cases were indistinguishable from those of infective hepatitis, post-arsphenamine jaundice, and homologous-serum jaundice admitted during the same period; hence it is unnecessary to describe the history of each case separately and in detail.

The initial symptoms were loss of appetite, abdominal discomfort, flatulence, nausea, and occasional vomiting, followed four or five days later by the onset of jaundice. On admission to hospital there were generally a slight fever for a few days, a moderate degree of icterus, and a palpable tender liver; the urine contained bile salts and bile pigments, and there was a moderate degree of granulopenia and also a raised icteric index or bilirubinaemia. One or two of these patients were seriously ill for a few days, but the majority of cases were quite mild; with strict bed rest the fever and other symptoms rapidly subsided, the jaundice cleared, and the patient was fit for discharge from hospital at the end of three or four weeks. There were no fatal cases. Table I gives a more detailed analysis of the cases seen.

TABLE I.—Analysis of Cases of Infective Hepatitis

Total number of cases of infective hepatitis	124
Number of these cases with a history of penicillin injections	
within the previous 7 months	36
Cases of gonorrhoea treated with penicillin*	9
Cases of syphilis treated with penicillin*	15
Cases of gunshot wounds treated with penicillin	2
Dermatological cases treated with penicillin	1
Cases of syphilis treated with penicillin but had injections of arsenic and bismuth	5
Cases of gunshot wounds treated with penicillin but had received blood or plasma transfusions	5

* One case is included in both these groups, as the patient had gonorrhoea and later syphilis within the relevant period; both these diseases were treated with penicillin.